

# Efficacy of Mirtazapine in Obstructive Sleep Apnea Syndrome

David W. Carley, PhD<sup>1-3</sup>; Christopher Olopade, MD<sup>2</sup>; Ge S. Ruigt, PhD<sup>4</sup>; Miodrag Radulovacki, MD, PhD<sup>2-3</sup>

<sup>1</sup>Center for Narcolepsy, Sleep and Health Research Departments of Medical-Surgical Nursing, <sup>2</sup>Medicine, and <sup>3</sup>Pharmacology, University of Illinois at Chicago, Chicago, IL; <sup>4</sup>Translational Research Department, NV Organon, Oss, The Netherlands

**Study Objectives:** Decreased serotonergic facilitation of upper-airway motor neurons during sleep has been postulated as an important mechanism rendering the upper airway vulnerable to obstruction in patients with obstructive sleep apnea syndrome (OSA). Although serotonin reuptake inhibitors have been shown to produce modest reductions in the apnea-hypopnea index (AHI) during non-rapid eye movement (NREM) sleep, they have not been proven to be generally effective as treatments for OSA. Conversely, antagonists of type 3 (5-HT<sub>3</sub>) serotonin receptors effectively have been shown to reduce the frequency of central apneas during rapid eye movement (REM) sleep in a rodent model of sleep-related breathing disorder. We sought to determine whether mirtazapine, a mixed 5-HT<sub>2</sub>/5-HT<sub>3</sub> antagonist that also promotes serotonin release in the brain would effectively reduce AHI during both NREM and REM sleep in patients with OSA.

**Design:** A randomized, double-blind, placebo-controlled, 3-way crossover study of mirtazapine in patients with OSA.

**Setting:** Laboratory studies were conducted in the Center for Sleep and Ventilatory Disorders at the University of Illinois Medical Center.

**Patients:** Seven adult men and 5 adult women with newly diagnosed (treatment-naïve) and medically uncomplicated OSA were randomized into the study.

**Interventions:** Each subject self-administered oral medications 30 minutes before bedtime each night for 3 consecutive 7-day treatment periods. These treatments comprised (1) placebo, (2) 4.5 mg per day of mirtazapine, and (3) 15 mg per day of mirtazapine. The order of treatments was randomized for each subject, and orders were counterbalanced for the

overall study.

**Measurements and Results:** Each subject charted his or her sleep-wake schedule throughout the study and completed the Stanford Sleepiness Scale every 2 hours during the seventh day of each treatment period. Subjects were studied by laboratory polysomnography on the seventh night of each treatment period. With respect to placebo treatment, 4.5 mg of mirtazapine significantly reduced the AHI in all sleep stages to 52%, with 11 of 12 subjects showing improvement over placebo; 15 mg of mirtazapine reduced the AHI to 46%, with 12 of 12 subjects showing improvement over placebo. Sleep fragmentation was reduced only by the higher dose of mirtazapine. Gross changes in sleep architecture were unremarkable.

**Conclusions:** Daily administration of 4.5 to 15 mg of mirtazapine for 1 week reduces AHI by half in adult patients with OSA. This represents the largest and most consistent drug-treatment effect demonstrated to date in a controlled trial. These findings suggest the therapeutic potential of mixed-profile serotonergic drugs in OSA and provide support for future studies with related formulations. Mirtazapine also is associated with sedation and weight gain—2 negative side effects in patients with OSA. In view of the above, we do not recommend use of mirtazapine as a treatment for OSA.

**Keywords:** Apnea, drug treatment, clinical trial, randomized, placebo-controlled, OSA, mirtazapine, serotonin

**Citation:** Carley DW; Olopade C; Ruigt GS et al. Efficacy of mirtazapine in obstructive sleep apnea syndrome. *SLEEP* 2007;30(1):35-41.

## EDITOR'S NOTE

The reader needs to be aware of the following information. On June 27, 2006, Cypress Bioscience Inc. announced "that the results of recently completed Phase IIa trials do not support continuing a development program evaluating combinations of mirtazapine with another approved drug as potential pharmaceutical

treatments for obstructive sleep apnea (OSA). Cypress and Organon, the human healthcare business unit of Akzo Nobel, had each independently conducted Phase IIa trials that served as the basis for today's announcement. A previous independently conducted small preliminary investigator sponsored pilot trial found that mirtazapine was able to reduce the number of abnormal respiratory events over the course of the night by roughly fifty percent. However, those data were not replicated in the recently completed phase IIa trials." (source: <http://www.cypressbio.com/news/releases/20060627.pdf>)

## Disclosure Statement

This investigator-initiated study was sponsored by NV Organon. Dr. Carley and Dr. Radulovacki have received additional research support from NV Organon and BTG International, and they have been compensated as scientific advisors to NV Organon. Dr. Carley and Dr. Radulovacki are named inventors of a technology for Pharmacologic Treatment for Sleep Apnea (U.S. Patents 6331536 and 6727242) assigned to The Board of Trustees of the University of Illinois (Chicago), which has licensed this technology to both Organon and BTG International. Dr. Ge S. Ruigt is a fulltime employee of NV Organon. Dr. Olopade had no other conflicts of interest.

Submitted for publication April 24, 2006

Accepted for publication August 28, 2006

Address correspondence to: David W. Carley, PhD, Professor and Director, Center for Narcolepsy, Sleep and Health Research, University of Illinois M/C 719, Room 910, 40 South Wood Street, Chicago, IL 60612; Tel: (312) 996-3827; Fax: (312) 996-4665; E-mail: [dwcarley@uic.edu](mailto:dwcarley@uic.edu)

## INTRODUCTION

THE PREVALENCE AND MORBID CONSEQUENCES ARISING FROM UNTREATED SLEEP-RELATED BREATHING DISORDERS (SRBDS) HAVE SPARKED AN ENORMOUS increase in investigations of these disorders over the past 4 decades. Despite the intensity of these efforts, the pathogenic mechanisms leading to SRBDs and their consequences remain poorly understood. Uncertainty regarding sleep-related changes in essential brainstem networks responsible for maintenance of both upper airway patency and a regular respiratory rhythm has hindered efforts to develop effective pharmacotherapeutics for SRBDs.<sup>1</sup> Over the past 15 years, several animal model systems have been developed to complement human investigations of SRBDs.<sup>2</sup>

Animal observations have suggested a putative therapeutic role for serotonin-promoting drugs in SRBDs. In particular, it is now established that during wakefulness serotonin,<sup>3</sup> most probably acting through 5-HT<sub>2A</sub> receptors,<sup>4</sup> provides a tonic excitatory input to hypoglossal motor neurons innervating the genioglossus and other upper airway dilating muscles. It follows that withdrawal of this serotonergic input during sleep might predispose to airway obstruction in the form of apnea or hypopnea. Accordingly, systemic administration of 5-HT<sub>2</sub> receptor antagonists to English bulldogs—an animal model of obstructive sleep apnea/hypopnea—reduced upper airway caliber and muscle tone.<sup>5</sup> Conversely, serotonin promotion by a combination of trazadone and l-tryptophan reduced the apnea-hypopnea index (AHI) in this model system.<sup>6</sup> This therapeutic rationale has been tested in both open-label and blinded placebo-controlled clinical studies designed to promote serotonergic activity in the brain. Collectively, studies using either serotonin precursors<sup>7</sup> or reuptake inhibitors<sup>8,9</sup> have demonstrated limited promise for reducing SRBD severity during non-rapid eye movement (NREM) sleep, but no benefit has been observed during rapid eye movement (REM) sleep.

We hypothesized that, in the above studies, a putative benefit of serotonin-enhancing drugs in the brain may have been offset by an apnea-promoting effect of serotonin in the peripheral nervous system. Intravenous serotonin injection in anesthetized cats and rats produces immediate dose-dependent apnea by activation of the Bezold-Jarisch reflex.<sup>10,11</sup> Intraperitoneal injection of serotonin produced no immediate apnea but caused an exacerbation of REM sleep-related apnea in a rodent model of central SRBD.<sup>12</sup> As discussed by the authors, this effect most likely was mediated by the action of serotonin at 5-HT<sub>3</sub> receptors on nodose ganglion cells. We subsequently screened a panel of 5-HT antagonist drugs, finding that ondansetron, a specific 5-HT<sub>3</sub> antagonist, reduced the frequency of spontaneous central apneas during REM but not NREM sleep.<sup>13</sup> Systemically delivered ondansetron was subsequently demonstrated to increase inspiratory activity in upper airway dilator motor neurons<sup>14</sup> and to reduce the frequency of apnea and hypopnea during REM sleep in the bulldog model of obstructive SRBD.<sup>15</sup> Conversely, mirtazapine, a mixed 5-HT<sub>2</sub>/5-HT<sub>3</sub> antagonist that also promotes serotonin release in the brain, reduced the expression of central apnea by 50% during both NREM and REM sleep in the rat model of SRBD.<sup>16</sup>

Here, we report the results of a double-blind, placebo-controlled, crossover study of 2 doses of mirtazapine on AHI in patients with obstructive sleep apnea (OSA) syndrome. As detailed below, mirtazapine again reduced AHI by approximately 50% during both NREM and REM sleep in this clinical pilot investigation.

## METHODS

Seven male and 5 female patients with obstructive sleep apnea-hypopnea syndrome<sup>17</sup> newly confirmed by polysomnography and naïve to any form of treatment participated in the present study. Subjects were aged from 18 to 67 years, and the mean age did not differ ( $p > 0.66$ ) between men ( $39.0 \pm 18.3$  [SD]) and women ( $43.4 \pm 14.2$ ). Two women were postmenopausal and 3 were premenopausal. Neither of the postmenopausal women was receiving hormone replacement therapy. The body mass index for men ( $32.3 \pm 9.7$  kg/m<sup>2</sup> [SD]) was significantly ( $p = 0.05$ ) lower than for the women ( $45.5 \pm 9.7$  kg/m<sup>2</sup>). Upon prestudy diagnostic poly-

somnography, all subjects met the criteria for a diagnosis of sleep apnea syndrome according to American Academy of Sleep Medicine guidelines<sup>17</sup> and were candidates for continuous positive airway pressure treatment (AHI for men =  $22.0 \pm 11.2$ ; women =  $24.1 \pm 22.8$ ). Significant cardiovascular, endocrine, hematologic, metabolic, neurologic, psychiatric, pulmonary, renal disorder, or sleep disorder other than obstructive sleep apnea (OSA), documented by history, physical, or laboratory examination, was excluded. Hypertension controlled to below 150 mm Hg systolic and 90 mm Hg diastolic by diuretics was permitted, but other antihypertensive regimens were excluded. Additional exclusion criteria included pregnancy, alcohol or drug abuse, a history of rotating or permanent night shift work within 6 months, and concomitant use of any central nervous system-active drug or any serotonergic drug. Before study entry, subjects received written and oral information and signed a consent document approved by the Institutional Review Board of the University of Illinois at Chicago. All procedures and protocols were conducted in compliance with the declaration of Helsinki and the standards of good clinical practice.

Upon meeting the above inclusion/exclusion criteria and providing informed consent, each subject participated in a randomized, double-blind, placebo-controlled, 3-way crossover study to evaluate the potential efficacy of mirtazapine (Remeron<sup>®</sup>, Organon, Oss, Netherlands) as a treatment for OSA. Daily mirtazapine doses (taken by mouth 30 minutes before bedtime) of 4.5 mg and 15 mg were compared to placebo. For this, each subject completed 3 consecutive 7-day treatment periods with no washout interval between periods. The treatment order was randomized for each subject, with each of the 6 possible treatment sequences represented twice among the overall subject group. Compliance was assessed by interview and by accounting of all returned treatment units.

Throughout all treatment periods, subjects charted their time in bed, estimated their sleep times, and completed questionnaires relating to sleep quality each morning. In addition, on the final (seventh) day of each treatment period, subjects completed a Stanford Sleepiness Scale<sup>18</sup> every 2 hours while they were awake. This scale provided a subjective introspective assessment of sleepiness rated on a scale of 1 (alert, wide awake, and energetic) to 7 (cannot stay awake, sleep onset soon).

Each subject underwent overnight polysomnography in the Center for Sleep and Ventilatory Disorders at the University of Illinois Hospital on the final day of each treatment period. Subjects reported to the Center at 9 pm and were instrumented for electroencephalograms (C4/A1, C3/A2), bilateral electrooculograms, electromyograms (submental, bilateral anterior tibial), electrocardiogram, oronasal airflow (thermistor, EPM Systems, Midlothian, VA), thoracoabdominal motions (piezo-crystal, EPM Systems), arterial oxygen saturation by pulse oximetry, and body position. All signals, including digital infrared video, were acquired, processed and stored by a Sleepscan system (Biologic Systems Corp., Mundelein, IL). Subjects were observed to take their medication (seventh dose) at 10:30 PM, and lights out was at 11:00 PM. All subjects were given an 8-hour sleep opportunity.

Sleep was scored according to standard criteria on 30-second epochs.<sup>19</sup> Electroencephalogram arousals were scored according to American Academy of Sleep Medicine guidelines<sup>20</sup> by a single polysomnographer blinded as to treatment and treatment-period. Time in bed was computed as the number of minutes in bed be-

tween lights out and lights on, total sleep time as the number of minutes of sleep between lights out and lights on, and sleep efficiency as the ratio of the two: total sleep time divided by time in bed. The distribution of sleep stages was separately determined as percentages of total sleep time scored as: (1) stage 1 or stage 2, (2) stage 3 or stage 4, and (3) REM sleep. Sleep latency was determined as the interval between lights out and the first of at least 3 successive epochs of sleep. REM sleep latency was determined as the interval between sleep onset and the first epoch of REM sleep.

Disordered breathing events were scored according to American Academy of Sleep Medicine guidelines<sup>17</sup> with 1 addition: apneas were defined as respiratory events in which oronasal airflow decreased by more than 90%, whereas hypopneas were defined as events in which airflow decreased by 90% or less. This addition was necessitated by the fact that the American Academy of Sleep Medicine criteria do not specify any cutoff for discriminating apneas from hypopneas. Rather, obstructive apnea-hypopnea events are defined together as a clear decrease (> 50%) in the amplitude of breathing during sleep.<sup>17</sup> Here, we scored hypopneas as clear decreases in airflow greater than 50% but less than 90% or as clear decreases less than 50% but associated with either an oxygen desaturation of more than 3% or an arousal.<sup>17</sup> Quantitative airflow measured by a sealed facemask and pneumotachograph must be viewed as the gold standard both for detecting sleep disordered breathing events and for discriminating apneas from hypopneas. No other current measurement technique is fully adequate for both detecting and discriminating these events. Oronasal thermistors have been viewed as a strong method to discriminate hypopneas from apneas but inferior to nasal pressure measurements for detecting events.<sup>17</sup>

In view of the above technologic limitations, and because AHI is a primary outcome variable, we sought to minimize variability of respiratory-event scoring by using a single polysomnographer blinded as to subject and treatment information. Additionally, after an interval of longer than 6 months, we had 5 randomly chosen records rescored by the initial polysomnographer and an additional polysomnographer. To evaluate scoring reliability, each epoch was recoded as having (1) apnea, (2) hypopnea, or (3) no event. In each case, the initial scoring by the primary polysomnographer was employed as the reference standard. Reference epochs scored as having multiple events were excluded from the analysis. This epoch-by-epoch comparison resulted in kappa coefficients of  $0.84 \pm 0.038$  for test-retest reliability and  $0.79 \pm 0.51$  for interrater reliability.

Statistical assessment of treatment effects on each study variable was performed using analysis of variance (ANOVA) with repeated measures. Planned contrasts between placebo and the 2 active treatments were controlled using the Fisher protected least significance difference (PLSD). ANOVA with repeated measures was also used to examine possible treatment order effects, and none were detected ( $p > 0.12$  for each variable). All statistical analyses were performed at the University of Illinois at Chicago in consultation with the General Clinical Research Center statistician.

## RESULTS

All twelve randomized subjects completed the trial, and no adverse events were reported. As summarized in Table 1, under

**Table 1**—Effects of Mirtazapine on Sleep, Breathing, and Alertness in Patients With Obstructive Sleep Apnea

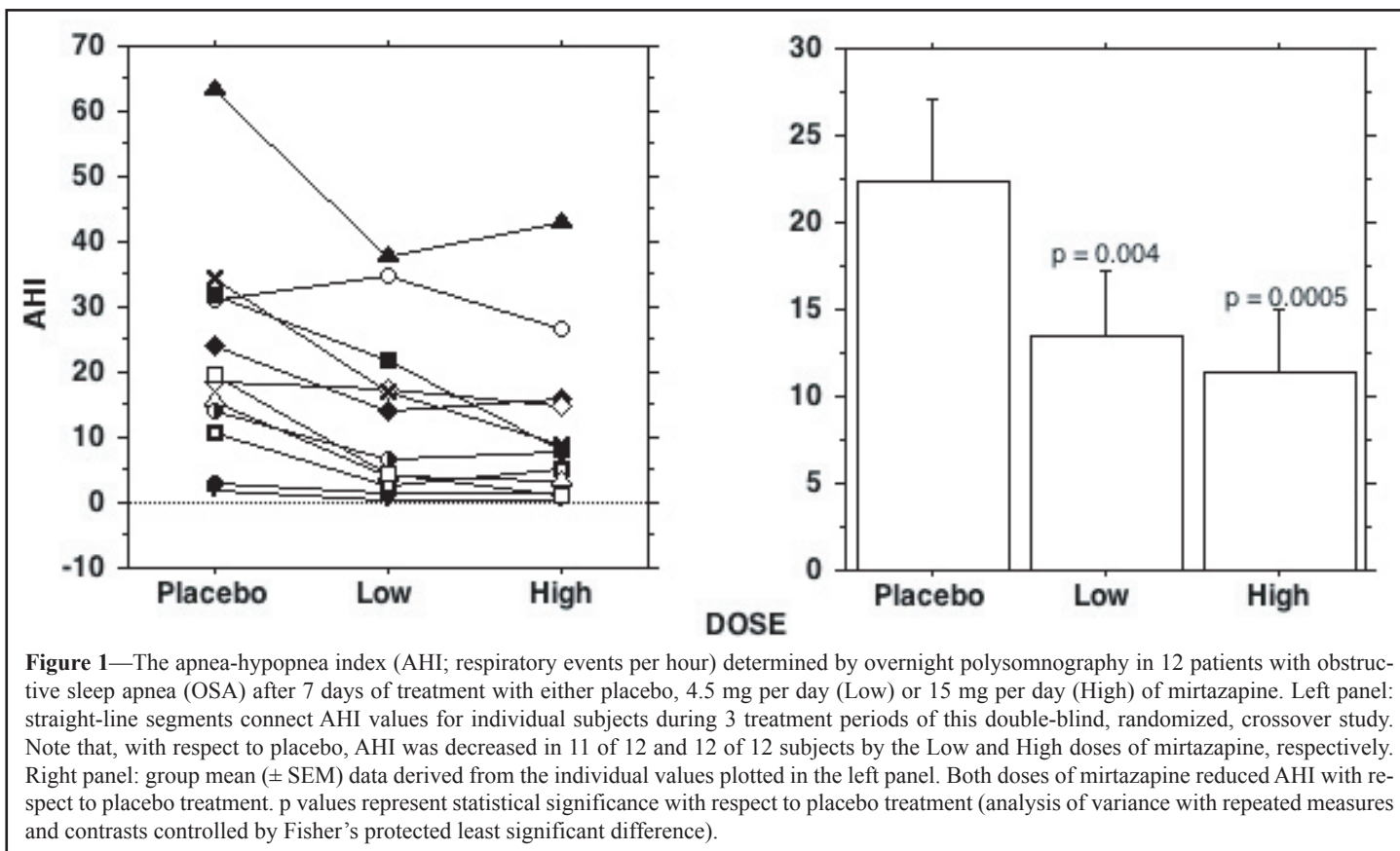
	Placebo	Mirtazapine		p Value
		4.5 mg QD	15 mg QD	
Sleep efficiency, %	82.9 ± 6.4	87.7 ± 4.9	90.1 ± 3.4 <sup>a</sup>	.05 <sup>a</sup>
Sleep latency, min	5.5 ± 1.3	3.8 ± 1.0	6.1 ± 1.8	
REM latency, min	88.5 ± 13.8	103.8 ± 19.3	82.9 ± 11.7	
Sleep stage, % of TST				
1 or 2	78.3 ± 3.2	76.9 ± 2.8	70.8 ± 2.6	
3 or 4	5.1 ± 1.9	7.5 ± 1.8	7.2 ± 2.2	
REM	16.6 ± 2.2	15.6 ± 1.3	22.2 ± 1.6 <sup>a</sup>	.04 <sup>a</sup>
Arousal Index, /h	41.1 ± 7.2	41.9 ± 9.4	28.1 ± 6.7 <sup>a</sup>	.02 <sup>a</sup>
Apnea Index, /h	9.0 ± 2.8	4.9 ± 1.9	5.4 ± 2.5	
Hypopnea Index, /h	13.3 ± 3.5	8.6 ± 2.6	6.0 ± 1.7 <sup>a</sup>	.02 <sup>a</sup>
AHI, /h	22.3 ± 4.8	13.5 ± 3.7 <sup>a</sup>	11.4 ± 3.6 <sup>a</sup>	.004 <sup>a</sup>
NREM AHI, /h	21.4 ± 5.1	13.6 ± 3.9 <sup>a</sup>	10.3 ± 3.0 <sup>a</sup>	.01 <sup>a</sup>
REM AHI, /h	26.8 ± 4.9	12.9 ± 3.4 <sup>a</sup>	15.3 ± 5.3 <sup>a</sup>	.01 <sup>a</sup>
AHI/Placebo AHI	1.0 ± 0	0.519 ± 0.086 <sup>a</sup>	0.460 ± 0.075 <sup>a</sup>	.0001 <sup>a</sup>
Minimum SaO <sub>2</sub>	81.7 ± 2.3	81.1 ± 2.7	80.8 ± 2.5	
ODI, >3%, /h	19.1 ± 4.8	10.6 ± 3.7	8.1 ± 3.1 <sup>a</sup>	.04 <sup>a</sup>
Stanford Sleepiness Scale	2.62 ± 0.34	2.18 ± 0.30	2.24 ± 0.33	

Data are presented as mean ± SEM for sleep, breathing, and subjective alertness variables in 12 subjects with obstructive sleep apnea syndrome. Each subject received each treatment for 7 days in randomized order and was studied by polysomnography at the end of each 7-day period. Treatment effects were tested by analysis of variance (ANOVA) with repeated measures. Planned comparisons of each active dose to placebo were controlled by Fisher protected least significant difference (PLSD). OSA refers to obstructive sleep apnea; REM, rapid eye movement sleep; TST, total sleep time; AHI, apnea-hypopnea index; NREM, non-rapid eye movement; ODI, oxygen desaturation index.

<sup>a</sup>p Value for statistical significance versus placebo, assessed by Fisher's PLSD. ANOVA demonstrated no significant treatment-period effects for any variable ( $p > .12$  for all).

placebo treatment, the mean apnea and hypopnea indexes were 9.0 (range: 0-30.2) and 13.3 (range: 0.8-44.1) per hour, respectively, while the AHI mean was 22.3 (range: 1.8-63.4), and the average minimum (nadir) oxygen saturation was 81.7%. Thus, the group of study subjects comprised newly diagnosed, medically uncomplicated patients with a wide range of severity in their OSA syndrome. Two subjects exhibited an AHI lower than 10 under placebo conditions: these subjects experienced 33 and 31 respiratory-event-related-arousals per hour, respectively. None of the significant findings detailed below were changed if these 2 subjects were excluded from the analysis.

Mirtazapine treatment at 15 mg per day reduced the hypopnea index by more than 50% ( $p = .02$ ; Table), but the decrease in the apnea index was not statistically significant ( $p = .16$ ) and nadir oxygen saturation during sleep was unchanged by either mirtazapine dose. However, as depicted in Figure 1 (left panel), the AHI was reduced with respect to placebo in 12 of 12 subjects during the 15 mg per day treatment period and in 11 of 12 subjects during the 4.5 mg per day treatment period. For the group, the mean AHI decreased from 22.3 for placebo treatment to 13.5 and 11.4 per hour for 4.5-mg and 15-mg doses, respectively (Figure 1, right panel). These treatment effects were highly significant ( $p \leq .004$  for each dose) when assessed by ANOVA with



**Figure 1**—The apnea-hypopnea index (AHI; respiratory events per hour) determined by overnight polysomnography in 12 patients with obstructive sleep apnea (OSA) after 7 days of treatment with either placebo, 4.5 mg per day (Low) or 15 mg per day (High) of mirtazapine. Left panel: straight-line segments connect AHI values for individual subjects during 3 treatment periods of this double-blind, randomized, crossover study. Note that, with respect to placebo, AHI was decreased in 11 of 12 and 12 of 12 subjects by the Low and High doses of mirtazapine, respectively. Right panel: group mean ( $\pm$  SEM) data derived from the individual values plotted in the left panel. Both doses of mirtazapine reduced AHI with respect to placebo treatment. *p* values represent statistical significance with respect to placebo treatment (analysis of variance with repeated measures and contrasts controlled by Fisher's protected least significant difference).

repeated measures. When computed relative to the AHI during placebo treatment for each subject, the AHI was reduced to 52% and 46% of the placebo level by 4.5 and 15 mg per day of mirtazapine, respectively (Table 1). Again, these treatment effects were highly significant ( $p < .0001$  for each). Five and 4 of the 12 subjects exhibited an AHI less than 5 during the 4.5-mg and 15-mg treatment periods, respectively. (Note that 2 of the 12 subjects exhibited an AHI  $< 5$  during all 3 period, including placebo, as described above).

The pattern of treatment-related decreases was observed for NREM-related AHI and REM-related AHI ( $p < .01$  for each; Table). Although subjects were not specifically instructed to sleep on their backs, analysis revealed that, on average, subjects spent  $88.2\% \pm 7.7\%$  of their sleep time in the supine position and that this was similar for all treatment periods ( $p > .5$ ). The main treatment effect on AHI was equivalent for supine and nonsupine positions ( $p > .1$  for the interaction of treatment  $\times$  position by ANOVA). Additionally, although the number of female subjects was too small for appropriate statistical analysis, the decreases in AHI for male and female subjects appeared similar ( $58.5\% \pm 11.6\%$  for men and  $47.5\% \pm 8.0\%$  for women). Further, the magnitude of the treatment effect (decrease in AHI with treatment) was significantly related to the baseline severity of the disorder (AHI during placebo treatment):  $r^2$  for 4.5 mg of mirtazapine was 0.75 ( $p < .0001$ ) and for 15 mg of mirtazapine was 0.79 ( $p < .0001$ ).

The effects of mirtazapine treatment on sleep architecture were less prominent. Sleep efficiency and REM sleep percentage were increased by both doses, although only the 15-mg per day effects achieved statistical significance ( $p = .05$  and  $p = .04$ , respectively; Table). In addition, the frequency of electroencephalographic arousals during sleep was decreased by 15 mg per day of mirtazapine to 65% of the placebo level ( $p = .02$ ; Figure 2). In con-

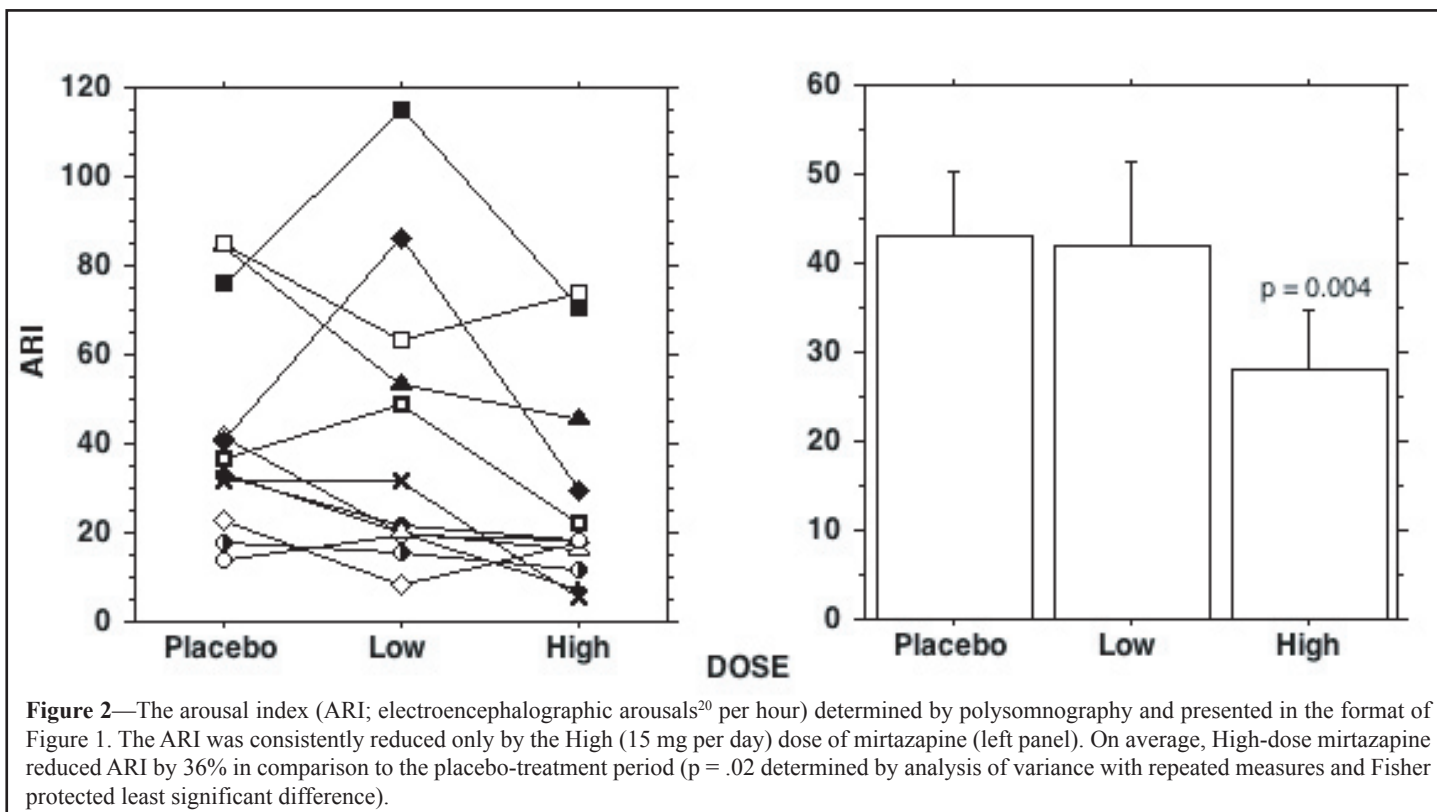
trast to the effects on AHI, the decrease in arousal frequency with treatment by 15 mg of mirtazapine was only weakly related to the baseline (placebo) arousal frequency:  $r^2 = 0.17$  ( $p = .04$ ). Mirtazapine had no effect on the expression of any stage of NREM sleep and did not alter sleep latency or the latency to REM sleep (Table).

Analysis of the Stanford Sleepiness Scales revealed that the subjects felt relatively alert throughout the daytime even during the placebo treatment periods. The mean score during placebo was 2.62 (Table 1), corresponding to a self-assessment falling between "functioning at a high level, but not at peak; able to concentrate" (scale score = 2) and "awake, but not fully alert" (scale score = 3). Treatment with 4.5- and 15-mg doses of mirtazapine numerically reduced the mean scores to 2.18 and 2.24, respectively, but these effects did not achieve statistical significance.

## DISCUSSION

The present double-blind, placebo-controlled, crossover study demonstrates that AHI is significantly reduced by oral mirtazapine in patients with OSA syndrome. This effect represents the largest and most consistent reduction of AHI so far demonstrated in any placebo-controlled test of a drug treatment for OSA. Another distinction from previous studies is that AHI was reduced to a similar extent during both NREM and REM sleep by mirtazapine, and this reduction was strongly correlated with the baseline severity of the AHI. Additionally, the treatment effects on AHI showed no clear body-position dependence and was similar among male and female subjects.

Despite the reduction in AHI during both active treatments (4.5-mg and 15-mg doses) with respect to placebo, the overnight nadir in oxygen saturation was unaffected by either dose of mirtazapine. This most probably reflects the fact that the residual



respiratory events were not shortened and, at least occasionally, were expressed in repetitive sequences such that the minimum oxygen saturation was not improved. Additionally, sleep quality and quantity were only slightly improved, despite a 50% reduction in respiratory events. Similarly, subjective daytime alertness was not significantly improved for either mirtazapine dose. Finally, it must be considered that the reduction in AHI could be an “artifact” of mirtazapine decreasing the number of arousals. However, this seems unlikely because, at the 4.5-mg dose, AHI and oxygen desaturation index were reduced by 48% and 44%, respectively, but the arousal index remain unchanged from placebo (Table 1).

Several previous studies have examined the effects of serotonin-related drugs in patients with OSA. Based on an uncontrolled study, Schmidt suggested that administration of the serotonin precursor l-tryptophan reduces sleep apnea<sup>7</sup> and Hanzel et al reported an unblinded clinical trial showing that the reuptake inhibitor fluoxetine reduced AHI during NREM sleep.<sup>8</sup> The latter finding was confirmed by Kraiczzi et al, who conducted a double-blind, placebo-controlled, crossover study of paroxetine. This study demonstrated a 19% decrease in AHI during NREM sleep, but neither the overall AHI nor the AHI during REM sleep was significantly reduced.<sup>9</sup>

Animal studies have provided both a motivation and a theoretical basis for interpreting the above studies. If OSA is viewed as a disorder of excessive sleep-related upper airway collapsibility, then any factor contributing to or amplifying the decreased activation of upper airway dilator muscles during sleep is a potential pathogenic factor for the disorder. Serotonin receptors are expressed on hypoglossal motor neurons innervating the genioglossus and other upper airway dilator muscles,<sup>21</sup> and activation of these receptors, particularly 5-HT<sub>2A</sub> receptors, is excitatory.<sup>4</sup> Further, with transitions from wake to NREM sleep, serotonin release from raphe neurons is reduced at various brainstem sites, including the hypoglossal motor nucleus, and release is minimal

during REM sleep.<sup>22-24</sup> These observations suggest that loss of serotonergic facilitation is one potential basis for the reduced upper airway muscle activation and increased collapsibility of the upper airway characteristic of REM sleep.

In this framework, the slight reduction in AHI during NREM sleep produced by serotonin reuptake inhibitors<sup>8,9</sup> could be attributed to increased activity of endogenous serotonin in the hypoglossal motor nuclei. It could be further reasoned that because serotonin release is at a minimum during REM sleep, these drugs would be expected to have little effect during this sleep state.<sup>9</sup> Still, more recent studies have questioned the importance of serotonergic inputs in the reduction of upper airway motor outputs during sleep, at least in the rat.<sup>3,25</sup> In any case, it is clear that systemic manipulations of the serotonergic system can lead to complex and poorly understood effects on respiratory and upper airway motor outputs. The net effects of such interventions are likely to be target-tissue and receptor-subtype specific.<sup>26</sup>

For example, although brainstem serotonin networks may increase upper airway motor outputs, it appears that they may also be important inhibitors of respiratory chemoreflexes.<sup>27</sup> Intracarotid 5-HT administration produces a biphasic ventilatory response comprising both excitation and inhibition,<sup>28</sup> whereas intravenous or intracardiac infusion produces immediate dose-dependent apnea, an effect dependent upon activation of 5-HT<sub>3</sub> receptors in or on nodose ganglion cell bodies.<sup>10</sup> Moreover, intraperitoneal administration of 5-HT in conscious rats produced a 3-fold increase in the apnea index during REM sleep.<sup>12</sup> This effect may also be attributable to nodose ganglion 5-HT<sub>3</sub> receptors because peripherally administered serotonin does not cross the blood-brain-barrier and because the effect was blocked by pretreatment with ondansetron,<sup>12</sup> a specific 5-HT<sub>3</sub> receptor antagonist that penetrates the brain only poorly.<sup>29</sup>

On this basis, we speculated that endogenous activation of serotonin receptors in the peripheral nervous system may predispose

to apnea, especially during REM sleep, whereas 5-HT activity in upper airway motor nuclei may protect against apnea, especially during NREM sleep. In accordance with this view, administration of ondansetron produced a dose-dependent REM sleep-specific suppression of apnea in the rodent<sup>12,30</sup> and bulldog<sup>15</sup> models of SRBD. Conversely, Stradling et al reported no effect of a single 16-mg dose of ondansetron on sleep architecture or disordered breathing in 10 patients with OSA.<sup>31</sup> The difference between these animal and human studies may reflect differing species, differing effective doses, or other factors. It is also possible that daily administration of ondansetron would produce greater effects than a single dose.<sup>32</sup> In any case, these studies serve collectively to underscore the potential complexities of serotonergic influences on sleep and breathing.

The present study represents the first controlled trial of a mixed-profile serotonergic agent in patients with OSA, though anecdotal evidence has been presented previously.<sup>33</sup> Mirtazapine is a potent 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptor antagonist but also promotes serotonin release in the brain by blocking presynaptic inhibitory adrenergic heteroreceptors on serotonergic nerve terminals.<sup>34-36</sup> Thus, the net serotonergic profile of mirtazapine is promotion of 5-HT<sub>1</sub> activity in the brain together with 5-HT<sub>2</sub>/5-HT<sub>3</sub> blockade in the central and peripheral nervous systems. In light of the conceptual framework presented above, we may speculate that the reduction of NREM AHI reported here reflected the change in 5-HT<sub>1</sub> activity in the brain. Consistent with this possibility is the report from Mendelson et al that the 5-HT<sub>1A</sub> agonist buspirone improved NREM AHI in 5 patients with OSA.<sup>37</sup> Also of note is the finding by Berry et al that mirtazapine doses similar (on a mg/kg basis) to those tested here produced augmentation of genioglossus activity in anesthetized rats, whereas, at higher doses, upper airway muscle activity was suppressed.<sup>38</sup> These and the present findings support the speculation that, at the doses tested, the ability of mirtazapine to increase brainstem serotonin or to block peripheral 5-HT<sub>3</sub> receptors predominated over blockade of central 5-HT<sub>2</sub> receptors. Moreover, Fenik et al demonstrated that blockade of 5-HT<sub>3</sub> receptors via systemic ondansetron resulted in increased upper airway dilator activity, supporting the view upper airway motor neurons in the medulla may be tonically inhibited by vagus nerve afferent fibers.<sup>14</sup> Further, we view that the reduction of AHI during REM sleep in the present study most probably reflected the antagonism of peripheral serotonin receptors by mirtazapine.

Still, the exact sites and relative importance of serotonergic effects for reducing AHI cannot be inferred from the present data. For example, 5-HT<sub>2</sub> and 5-HT<sub>3</sub> antagonism may have accentuated the 5-HT<sub>1</sub>-mediated effects in the ventral respiratory group of the medulla. Also, we tested racemic mirtazapine, comprising an equal mixture of (+) and (-) enantiomers. However, these enantiomers have a differential pharmacology,<sup>36</sup> and direct comparative tests of these isomers in both animal and human trials may help to elucidate the mechanisms by which mirtazapine influences respiration. Additionally, we cannot rule out other mechanisms, including the actions of mirtazapine at other targets, such as adrenergic autoreceptors or histamine receptors. The reduction of disordered respiration was not a result of changes in sleep architecture. Gross sleep architecture (Table) and microarchitecture (electroencephalogram arousals; Figure 2) were unchanged by 4.5 mg per day of mirtazapine, yet this dose was associated with a nearly 50% reduction in AHI.

Two limitations of the present study are immediately relevant

to interpretation of the findings. First, the treatment periods were only 7 days. Due to the crossover study design, the delay in institution of conventional treatment for these patients with OSA was therefore 21 to 28 days; an interval deemed to be acceptable by the University of Illinois at Chicago Institutional Review Board. The decision to reduce the treatment period to 7 days was based on clinical data regarding the pharmacokinetics and onset of antidepressant action for mirtazapine. Steady-state plasma levels of mirtazapine are achieved within 4 days in adults taking a single daily dose.<sup>39</sup> Furthermore, although the antidepressant effect of mirtazapine is not fully manifest until 14 to 28 days after initial dosing, there are clinically and statistically significant effects as early as the fourth day of treatment.<sup>40</sup> Therefore it is reasonable to attribute the present reduction in AHI to the pharmacologic effects of mirtazapine on the central and peripheral nervous systems, but the present study may have underestimated the potential magnitude of reduction achievable under long-term treatment.

The study also is limited by the fact that washout periods were not included between treatment periods. Again, this decision was made to minimize the delay to institution of conventional treatment. Based on the pharmacokinetics of mirtazapine, we expect that steady-state plasma levels were achieved by day 4 of each treatment period. Similarly, the elimination half-life of 20 to 40 hours<sup>41</sup> is in agreement with the view that a new and steady-state plasma level would be established within 4 days following crossover, even without an explicit washout period. Despite this, and the absence of a statistically significant treatment-order effect, we cannot completely rule out carryover effects due to the relatively limited number of subjects. We specifically examined the data for treatment-order effects, and none were detected by ANOVA with repeated measures and posthoc contrasts controlled by Fisher's PLSD ( $p > .12$  for each variable). In addition, carryover effects between treatment periods, if present, would have led us to underestimate the true treatment effects because the treatment sequences were counterbalanced.

Although this is the first controlled human trial, effects of mirtazapine on SRBD have been reported. In a case report of an 84-year-old man, Castillo et al described a reduction in AHI from 54.9 to 9.3 after 3 months of treatment with 15 mg daily of mirtazapine.<sup>33</sup> In the rodent model of central SRBD, we described an approximate 50% reduction in the apnea index over a 50-fold dose range of mirtazapine.<sup>16</sup> Despite the fact that rats express central apneas, the similar effects of mirtazapine in rat and man suggest the potential utility of the rodent model of SRBD as a screening tool to identify pharmacotherapeutic candidates for OSA.

In summary, the present study demonstrates the largest and most consistent improvement in AHI in a controlled trial for any drug to date—AHI was reduced by approximately 50% during all sleep stages. This finding supports the principle of treating OSA using mixed-profile serotonergic drugs. Despite the fact that all subjects demonstrated improvement with treatment, the AHI remained above 5 in a majority of subjects, sleep remained significantly fragmented, and slow-wave sleep time remained below normal. Mirtazapine also is associated with sedation and weight gain—2 negative side effects in patients with OSA. In view of the above, we do not recommend the use of mirtazapine as a treatment for OSA. Additional studies to evaluate other formulations designed to improve the responder rate and to decrease the negative side-effect potential will be necessary.

## REFERENCES

1. Veasey SC. Pharmacotherapies for obstructive sleep apnea: how close are we? *Curr Opin Pulm Med* 2001;7:399-403.
2. Carley D, Radulovacki M, eds. *Sleep-Related Breathing Disorders: Experimental Models and Therapeutic Potential*. Vol. 171. New York: Marcel Dekker; 2003.
3. Sood S, Morrison JL, Liu H, Horner RL. Role of endogenous serotonin in modulating genioglossus muscle activity in awake and sleeping rats. *Am J Respir Crit Care Med* 2005;172:1338-47.
4. Fenik P, Veasey SC. Pharmacological characterization of serotonergic receptor activity in the hypoglossal nucleus. *Am J Respir Crit Care Med* 2003;167:563-9.
5. Veasey SC, Panckeri KA, Hoffman EA, Pack AI, Hendricks JC. The effects of serotonin antagonists in an animal model of sleep-disordered breathing. *Am J Respir Crit Care Med* 1996;153:776-86.
6. Veasey SC, Fenik P, Panckeri K, Pack AI, Hendricks JC. The effects of trazodone with L-tryptophan on sleep-disordered breathing in the English bulldog. *Am J Respir Crit Care Med* 1999;160:1659-67.
7. Schmidt H. L-tryptophan in the treatment of impaired respiration in sleep. *Bull Eur Physiopathol Respir* 1983;19:625-9.
8. Hanzel D, Proia N, Hudgel DW. Response of obstructive sleep apnea to fluoxetine and protriptyline. *Chest* 1991;100:416-21.
9. Kraiczi H, Hedner J, Dahlof P, Ejnell H, Carlson J. Effect of serotonin uptake inhibition on breathing during sleep and daytime symptoms in obstructive sleep apnea. *Sleep* 1999;22:61-6.
10. Yoshioka M, Goda Y, Togashi H. Pharmacological characterization of 5-hydroxytryptamine-induced apnea in the rat. *J Pharmacol Exp Ther* 1992;260:917-24.
11. Jacobs L, Comroe JH. Reflex apnea, bradycardia, and hypotension produced by serotonin in cats. *Circ Res* 1971;29:145-55.
12. Carley DW, Radulovacki M. Role of peripheral serotonin in the regulation of central sleep apneas in rats. *Chest* 1999;115:1397-401.
13. Radulovacki M, Trbovic SM, Carley DW. Serotonin 5-HT<sub>3</sub>-receptor antagonist GR 38032F suppresses sleep apneas in rats. *Sleep* 1998;21:131-6.
14. Fenik P, Ogawa H, Veasey SC. Hypoglossal nerve response to 5-HT<sub>3</sub> drugs injected into the XII nucleus and vena cava in the rat. *Sleep* 2001;24:871-8.
15. Veasey SC, Chachkes J, Fenik P, Hendricks JC. The effects of ondansetron on sleep-disordered breathing in the English bulldog. *Sleep* 2001;24:155-60.
16. Carley DW, Radulovacki M. Mirtazapine, a mixed-profile serotonin agonist/antagonist, suppresses sleep apnea in the rat. *Am J Respir Crit Care Med* 1999;160:1824-9.
17. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999;22:667-89.
18. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of sleepiness: a new approach. *Psychophysiology* 1973;10:431-6.
19. Rechtschaffen A, Kales A. *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects* Los Angeles: Brain Information Service/Brain Research Institute UCLA; 1968.
20. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep* 1992;15:173-84.
21. Okabe S, Mackiewicz M, Kubin L. Serotonin receptor mRNA expression in the hypoglossal motor nucleus. *Respir Physiol* 1997;110:151-60.
22. Strecker RE, Thakkar MM, Porkka-Heiskanen T, Dauphin LJ, Bjorkum AA, McCarley RW. Behavioral state-related changes of extracellular serotonin concentration in the pedunculopontine tegmental nucleus: a microdialysis study in freely moving animals. *Sleep Res Online* 1999;2:21-7.
23. Blanco-Centurion CA, Salin-Pascual RJ. Extracellular serotonin levels in the medullary reticular formation during normal sleep and after REM sleep deprivation. *Brain Res* 2001;923:128-36.
24. Lai YY, Kodama T, Siegel JM. Changes in monoamine release in the ventral horn and hypoglossal nucleus linked to pontine inhibition of muscle tone: an in vivo microdialysis study. *J Neurosci* 2001;21:7384-91.
25. Sood S, Raddatz E, Liu X, Liu H, Horner RL. Inhibition of serotonergic medullary raphe obscurus neurons suppresses genioglossus and diaphragm activities in anesthetized but not conscious rats. *J Appl Physiol* 2006;100:1807-21.
26. Veasey SC. Serotonin agonists and antagonists in obstructive sleep apnea: therapeutic potential. *Am J Respir Med* 2003;2:21-9.
27. Martin-Body RL, Grundy HR. Effects of neurotoxin-induced brainstem lesions on the respiratory responses of conscious rats. *Clin Exp Pharmacol Physiol* 1985;12:427-37.
28. Matsumoto S. Effects of carotid body chemoreceptor stimulation by 5-HT on phrenic nerve activity and ventilation in the rabbit. *Arch Int Pharmacodynam Ther* 1981;254:282-92.
29. Simpson KH, Murphy P, Colthup PV, Whelan P. Concentration of ondansetron in cerebrospinal fluid following oral dosing in volunteers. *Psychopharmacology (Berl)* 1992;109:497-8.
30. Carley D, Olopade S, Seink S, Radulovacki M. Serotonin antagonist improves obstructive sleep apnea. *Sleep Med* 2003;4:S6.
31. Stradling J, Smith D, Radulovacki M, Carley D. Effect of ondansetron on moderate obstructive sleep apnoea, a single night, placebo-controlled trial. *J Sleep Res* 2003;12:169-70.
32. Faris PL, Kim SW, Meller WH, et al. Effect of decreasing afferent vagal activity with ondansetron on symptoms of bulimia nervosa: a randomised, double-blind trial. *Lancet* 2000;355:792-7.
33. Castillo JL, Menendez P, Segovia L, Guillemainault C. Effectiveness of mirtazapine in the treatment of sleep apnea/hypopnea syndrome (SAHS). *Sleep Med* 2004;5:507-8.
34. de Boer TH, Maura G, Raiteri M, de Vos CJ, Wieringa J, Pinder RM. Neurochemical and autonomic pharmacological profiles of the 6-aza-analogue of mianserin, Org 3770, and its enantiomers. *Neuropharmacology* 1988;27:399-408.
35. de Boer T. The pharmacologic profile of mirtazapine. *J Clin Psychiatry* 1996;57:19-25.
36. DeVane CL. Differential pharmacology of newer antidepressants. *J Clin Psychiatry* 1998;59 Suppl 20:85-93.
37. Mendelson WB, Maczaj M, Holt J. Buspirone administration to sleep apnea patients. *J Clin Psychopharmacol* 1991;11:71-2.
38. Berry RB, Koch GL, Hayward LF. Low-dose mirtazapine increases genioglossus activity in the anesthetized rat. *Sleep* 2005;28:78-84.
39. Anttila SA, Leinonen EV. A review of the pharmacological and clinical profile of mirtazapine. *CNS Drug Rev* 2001;7:249-64.
40. Behnke K, Sogaard J, Martin S, et al. Mirtazapine orally disintegrating tablet versus sertraline: a prospective onset of action study. *J Clin Psychopharmacol* 2003;23:358-64.
41. Timmer CJ, Sitsen JM, Delbressine LP. Clinical pharmacokinetics of mirtazapine. *Clin Pharmacokinetics* 2000;38:461-74.